REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-8 are in this case. Claim 1-8 have been rejected. Claims 2-3 and 5-8 have now been canceled. Claims 1 and 4 have now been amended.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 1-8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner's rejections are respectfully traversed. Claims 1 and 4 have now been amended. Claims 2-3 and 5-8 have now been canceled, rendering moot the Examiner's rejection of these claims.

The Examiner contends that the method lacks a conclusion step which indicates that inhibiting has occurred and indicates how inhibition is determined or what the result is.

While Applicant disagrees with the Examiner's contention that the method lacks a conclusion step which indicates that inhibiting has occurred and indicates how inhibition is determined or what the result is, in the interest of expediting prosecution in this case, Applicant currently elects to amend claim 1 to now recite:

> *"A method of inhibiting HBV attachment to a hepatic cell, the method comprising exposing the cell to a polypeptide capable of binding the preS1 region of HBV and having an amino acid sequence at least 90% homologous to the amino acid sequence set forth in SEQ ID NO: 4 as determined using the Bestfit software of the GCG package set with a gap creation penalty of 50 and a gap extension penalty of 3, thereby inhibiting HBV attachment to a hepatic cell."*

Applicant wishes to point out that claim 1 as currently amended now includes a conclusion step which more clearly indicates that inhibiting has occurred and indicates how inhibition is determined or what the result is.

In any case, Applicant wishes to respectfully further point out that Currently

Amended claim 1 now corresponds identically to claim 1 of corresponding U.S. Patent No. 6,589,534 issued from U.S. Patent Application No. 09/409,096 having an essentially identical specification as that of the present application, with the only difference in the presently amended claim being the recitation "SEQ ID NO: 2" of the U.S patent claim being substituted with the recitation "SEQ ID NO: 4". As clearly shown in the Examples section of the specification SEQ ID NOs: 2 and 4 correspond to polypeptides (UP43 and UP50, respectively) both share the essentially identical relevant functionality of the present invention, namely of being capable of specifically binding amino acids 21-49 of the HBV receptor binding region (preS1) of HBsAg, and to intact HBV particles. Thus, with respect to the requirements of 35 U.S.C. § 112, second paragraph, currently amended claim 1 is essentially identical to claim 1 of the corresponding U.S. patent having issued by virtue of fulfilling the requirements of 35 U.S.C. § 112, second paragraph.

In view of the arguments and amendments set forth above, Applicant believes to have overcome the 35 U.S.C. § 112, second paragraph, rejections.

35 U.S.C. § 112, First Paragraph, Enablement Rejections

The Examiner has rejected claims 1-8 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 4 binding to a portion of HBV preS1 (as defined by SEQ ID NOs: 8 and 9), does not reasonably provide enablement for *in-vivo* activity, prevention of disease, and 60 percent homologous regions, portions, or whole SEQ ID NO: 4 that function to inhibit attachment. The Examiner states that the specification does not enable any skilled person in the art to which it pertains, or with which it is most closely connected, to use the invention commensurate in scope with these claims. The Examiner's rejections are respectfully traversed. Claims 1 and 4 have now been amended. Claims 2-3 and 5-8 have now been canceled, rendering moot the Examiner's rejection of these claims.

The Examiner states that the specification does not provide any working examples that would indicate that the claimed method is able to be administered to an animal in such a way that they will be effective at inhibiting attachment of HBV to hepatic cells. The Examiner concedes that the specification provides evidence under *in-vitro* experimental conditions that SEQ ID NO: 4 binds to the preS1 region

included in SEQ ID NOs: 8 and 9, but does not teach how a pharmaceutical composition including SEQ ID NO: 4 would be administered in such a way as to function, and does not provide sufficient guidance to allow one skilled in the art to use the claimed method to inhibit the binding of HBV to hepatic cells *in-vivo*. The Examiner states that there is a difference between *in-vivo* and *in-vitro* methods, and that this is an area of great unpredictability. The Examiner contends that this unpredictability and lack of correlation between *in-vivo* and *in-vitro* is shown by Mitsuya *et al.* which teaches that the reverse transcriptase (RT)-inhibitor suramin functions *in-vitro* at concentrations attainable *in-vivo*, and Sandstrom *et al.* which teaches that suramin was discontinued from clinical use due to adverse side-effects and no strong showing of effective reduction of infectious virus.

The Examiner concedes that one polypeptide, such as an antibody, can bind virus so as to prevent attachment/infection of a cell, but stipulates that another polypeptide binding a same protein may bind but not block attachment and allow infection of a cell. The Examiner states that the specification has not shown that the SEQ ID NO: 4 polypeptide actually inhibits binding of HBV to hepatic cells, and that the specification infers this from the binding of SEQ ID NOs: 8 and 9. The Examiner asserts that it is not shown that the binding epitope used by this polypeptide will result in blockage of attachment or if binding leaves available "another side" of the virus to bind hepatic cells. The Examiner states that there is more than one epitope on the peptides used to screen for SEQ ID NO: 4, and that there is no showing that the epitope bound is the same as shown in the prior art (Neurath *et al.*).

The Examiner asserts that the art is unclear whether there is a single receptor for HBV and that there may be more, based on Meyer *et al.*, page 147, last paragraph-end of page 148.

The Examiner states that the specification does not disclose the specific binding motif on the SEQ ID NO: 4 polypeptide that binds to the known peptides. The Examiner asserts that the characteristics of the proteins as recited in claim 8 do not enable one to a more refined area of search to find other proteins, and that the claimed characteristics of claim 8 have not been shown to be relevant to inhibiting binding. The Examiner states that the claimed invention is not enabled for recombinant urinary protein comprising portions and 60 percent homologous proteins for inhibiting HBV binding to hepatic cells.

Applicant respectfully disagrees with the Examiner's contention that the specification does not enable any skilled person in the art to which it pertains, or with which it is most closely connected, to use the invention commensurate in scope with claims 1-8. Nevertheless, in the interest of expediting prosecution of the instant application, Applicant currently elects to amend claim 1, as described above, and similarly claim 4, to recite the identical claim language of claims 1 and 2, respectively, of the issued corresponding U.S. patent application, with the exception of the recitation "SEQ ID NO: 2" of the corresponding patent being replaced in Currently Amended claims 1 and 4 with "SEQ ID NO: 4". As described above, SEQ ID NOs: 2 and 4 correspond to polypeptides (UP43 and UP50, respectively) both share the essentially identical relevant functionality of the present invention, namely of being capable of specifically binding amino acids 21-49 of the HBV receptor binding region (preS1) of HBsAg and to intact HBV particles. Thus, with respect to the requirements of 35 U.S.C. § 112, first paragraph, Currently Amended claims 1 and 4 are essentially identical to claims 1 and 2 of the corresponding U.S. patent having issued by virtue of fulfilling the requirements of 35 U.S.C. § 112, first paragraph. In the further interest of expediting prosecution of the instant application, Applicant further currently elects to cancel claims 2-3 and 5-8.

Applicant disagrees with the Examiner's contention, supported by the cited Mitsuya *et al.* and Sandstrom *et al.* references, teach that the claimed *in-vivo* treatment method will have unpredictable results and is respectfully of the opinion that the cited references do not teach that the *in-vitro* experimental results of the present specification cannot be reliably extrapolated to therapeutic *in-vivo* results. Applicant wishes to respectfully point out that Sandstrom *et al.* teaches that suramin indeed demonstrated desired effects *in-vivo* in HIV-infected patients, such as virus-negative blood cultures (Sandstrom *et al.*, page 376, column 2, first paragraph), and that the concluding teachings of Sandstrom *et al.* did not exclude use of suramin for therapeutic use *in-vivo*, but simply conclude that: "*Suramin is no longer being considered as a single-drug treatment modality.*" (Sandstrom *et al.*, page 376, "Adverse Effects" section). The validity of using RT inhibitors, the class of drugs to which suramin belongs, in combination with other drugs for treatment of HIV infection has clearly been corroborated by the state-of-the-art treatment of HIV infection [highly active antiretroviral therapy (HAART)] which employs an RT-

inhibitor as a mandatory component of a multi-drug cocktail (for example, refer to enclosed abstract of Sharma *et al.*). Furthermore, applicant wishes to respectfully point out that the adverse effects of suramin *in-vivo*, which were postulated as unpredictable by the Examiner, were in fact clearly predicted in the context of treatment of HIV-infected patients at the time of the *in-vitro* studies (Mitsuya *et al.*, final paragraph). Moreover, the cited references relate to a therapeutic compound, suramin, which, by virtue of being foreign to the human body, is inherently more likely to be toxic than SEQ ID NO: 4 which is found in urine, as described in the Examples section of the specification.

Applicant is respectfully of the opinion that the cited references in any case do not teach the unpredictability of using SEQ ID NO: 4 *in-vivo* to treat HBV infection due to further critical and relevant differences between the context of the cited references and that of the claimed invention. The cited references relate to HIV infection which is a pathology having profound and relevant differences relative to HBV. Treatment of HIV infection is well known as being one of the most difficult types of viral infections to treat due, despite decades of massive research efforts aimed at finding a suitable treatment. This is due to the very particular characteristics of HIV which primarily targets the immune system itself, and which is characterized by an extremely high rate of adaptive mutation (for example, refer to enclosed abstract of Mosier *et al.*). In very sharp contrast, HBV does not target the immune system itself, but rather liver cells, and is not characterized by the extreme adaptive mutability of HIV. As such, the cited references, by virtue of relating to treatment of HIV infection as opposed to treatment of HBV infection, do not teach that *in-vivo* treatment of HBV infection based on the *in-vitro* experimental results of the specification will achieve unpredictable results. Moreover, the cited references relate to suramin which, by virtue of being an inhibitor of an intracellular enzyme (HIV reverse transcriptase), must achieve intracellular penetration to be able to exert inhibition of RT, and even then only in cells in which viral entry, the first major phase of viral infection, has already occurred. In critically sharp contrast, however, SEQ ID NO: 4, by virtue of being an inhibitor of a viral receptor ligand-viral receptor interaction, inherently exerts is inhibitory activity extracellularly, and hence does not require intracellular penetration and may exert its activity so as to prevent infection of healthy cells prior to viral entry. For such reasons, therefore, treatment of HIV

infection using suramin is mechanistically unrelated to, and is inherently much more difficult to achieve compared to, treating HBV infection using SEQ ID NO: 4. Therefore, Applicant is of the strong opinion that the cited references, by virtue of relating to an RT inhibitor of HIV infection, as opposed to the HBV receptor binding inhibitor of the claimed invention, do not teach that *in-vivo* treatment of HBV infection based on the *in-vitro* experimental results of the specification will be unpredictable.

Applicant respectfully disagrees with the Examiner's contention that the specification does not teach how a pharmaceutical composition including SEQ ID NO: 4 would be administered in such a way as to function, and thereby fails to fulfill the requirements of 35 U.S.C. § 112, first paragraph. In this regard Applicant wishes to respectfully point out that, as conceded by the Examiner in the present communication, an antibody, which is a polypeptide similarly to SEQ ID NO: 4, may indeed be used to bind a viral receptor ligand in such a way as to prevent cellular attachment/infection. Furthermore, the art at the time of the claimed invention indeed clearly teaches how to administer antibodies so as to prevent/treat HBV infection (refer, for example, to enclosed abstract of de Man *et al.*). As such, Applicant is of the strong opinion that at the time of the claimed invention it would have been well within the purview of one of ordinary skill in the art to administer a polypeptide such as SEQ ID NO: 4 so as to successfully prevent cellular attachment/infection of HBV *in-vivo*, and hence to successfully treat HBV infection *in-vivo*.

Applicant respectfully disagrees with the Examiner's contention that the claimed method does not fulfill the requirements of 35 U.S.C. § 112, First Paragraph based upon arguments to the effect that the specification has not shown that the SEQ ID NO: 4 polypeptide actually inhibits binding of HBV to hepatic cells, that the binding epitope used by this polypeptide will result in blockage of attachment or if binding leaves available "another side" of the virus to bind hepatic cells, and that there is more than one epitope on the peptides used to screen for SEQ ID NO: 4, and that there is no showing that the epitope bound is the same as shown in the prior art. Applicant wishes to respectfully point out that the capacity of the SEQ ID NO: 4 polypeptide to specifically bind to both a purified peptide encompassing amino acids 21-49 of preS1 and to intact HBV particles clearly indicates that this polypeptide is capable of blocking HBV infection since as shown in the literature (refer, for

example, to enclosed article of Seyec *et al.*) any mutation/deletion of an amino acid which lies within a region encompassed by amino acids 3-77 of the preS1 region leads to abolishment of infection. It should be noted that this study does not contradict prior art studies but rather substantiates prior art findings with respect to HBV-hepatocyte interactions, as is clear from the abstract section which states: *"These results confirm the involvement of the L protein in the infection step and demonstrate that the sequence between amino acids 3 and 77 is involved in this process."* Since the SEQ ID NO: 4 polypeptide binds and thus effectively masks at least amino acids 21-49 of the preS1 region, and since these amino acids lie within the region identified by Le Seyec et al. as being involved in HBV-hepatocyte interactions and infection, it is Applicant's strong opinion that the proteins of the present invention would indeed block HBV infection and that one of ordinary skill in the art would indeed have a reasonable expectation of success when applying the teachings of the present invention to prevention of HBV infection.

Applicant respectfully disagrees with the Examiner's contention that the claimed method does not fulfill the requirements of 35 U.S.C. § 112, first paragraph based on the argument there may exist multiple receptors for HBV. In this regard Applicant wishes to respectfully point out that total blockage of viral infection *in-vivo* is not required for achieving therapeutic effect, since, for example, slowing down the kinetics of viral infection, such as HBV infection, will be well understood as resulting in attenuation of HBV-mediated pathogenesis, and facilitation/acceleration of therapeutic immune rejection of the virus (refer, for example, to enclosed abstract of Bertoletti and Ferrari, and enclosed article of Whalley *et al.*).

Applicant respectfully disagrees with the Examiner's contention that claim 8 does not fulfill the requirements of 35 U.S.C. § 112, first paragraph, on the basis of arguments to the effect that the characteristics of the proteins as recited in claim 8 do not enable one to a more refined area of search to find other proteins, and that the claimed characteristics of claim 8 have not been shown to be relevant to inhibiting binding. Nevertheless, in the interest of expediting prosecution of the instant application, Applicant currently elects to amend claim 4 and cancel claim 8, as mentioned hereinabove.

Applicant respectfully disagrees with the Examiner's contention that the claimed invention does not fulfill the requirements of 35 U.S.C. § 112, first

paragraph, on the basis of argumentation to the effect that the specification does not disclose the specific binding motif on the SEQ ID NO: 4 polypeptide that binds to the known peptides, and that the claimed invention is not enabled for recombinant urinary protein comprising portions and 60 percent homologous proteins for inhibiting HBV binding to hepatic cells. Nevertheless, in the interest of expediting prosecution of the instant application, Applicant currently elects to file claims drawn to a polypeptide capable of binding the preS1 region of HBV and having an amino acid sequence which is at least 90 percent homologous to the amino acid sequence set forth in SEQ ID NO: 4. Specification support for the recitation of: a polypeptide capable of binding the preS1 region of HBV and having an amino acid sequence which is at least 90 percent homologous to the amino acid sequence set forth in SEQ ID NO: 4; can be found, for example, at page 14, second paragraph, line 24, and in the original recitation of a range of at least 60 percent. Applicant wishes to point out that according to MPEP 2163.05 (III Range Limitations) it is permissible under 35 U.S.C. § 112, first paragraph to amend claims to recite numerical ranges, such as the range of at least 90 percent which is included in the numerical range of at least 60 percent disclosed in the original specification. MPEP 2163.05 (III Range Limitations) recites the following:

> *"In the decision in In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%-60%" and specific examples of "36%" and "50%." A corresponding new claim limitation... to "between 35% and 60%" did meet the description requirement."*

In view of the above arguments and claim amendments, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 112, First Paragraph, Written Description Rejections

The Examiner has rejected claims 1-8 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, and as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the

application was filed, had possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 1 and 4 have now been amended. Claims 2-3 and 5-8 have now been canceled, rendering moot the Examiner's rejection of these claims.

In particular, the Examiner contends that the burden of the written description in this application is for recombinant urine derived proteins that bind an HBV preS1 peptide and inhibit the binding of HBV to hepatic cells and a whole range of nucleotide sequences that encode proteins. The Examiner states that the written description in this case only sets forth two proteins that bind the HBV peptide. The Examiner states that with the exception of two proteins disclosed, the skilled artisan cannot envision all the encompassed proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. The Examiner asserts that the two proteins disclosed are not very related by homology and it is not disclosed what is the critical binding region or any specific showing that the protein inhibits binding of HBV to hepatic cells. The Examiner further states that without knowing more of what is required for the composition of claim 1, the coding sequences of claim 3, parts b and c, are not fully described either. The Examiner continues with the assertion that polynucleotides that are related by percent identity of hybridization conditions allow for alteration of too many amino acid residues to retain the ability to bind to the HBV peptide especially in view of not knowing what sequence is important. The Examiner concludes that therefore that only the recombinant urine-derived protein of SEQ ID NO: 4 is described, but that the full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph.

Applicant respectfully disagrees with the Examiner's contention that the claimed invention fails to comply with the written description requirement, and thereby contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Nevertheless, in the interest of expediting prosecution of the instant application, Applicant currently elects to amend claims 1 and 4, as described hereinabove, to recite the identical claim language of claims 1 and 2, respectively, of the issued corresponding U.S. patent application, with the irrelevant exception of the recitation "SEQ ID NO: 2" of the

corresponding patent claims being replaced in Currently Amended claims 1 and 4 with "SEQ ID NO: 4". Further in the interest of expediting prosecution of the instant application, Applicant currently elects to cancel claims 2-3 and 5-8. Applicant therefore currently elects to file claims, which as described hereinabove, are drawn to a polypeptide capable of binding the preS1 region of HBV and having an amino acid sequence at least 90% homologous to the amino acid sequence set forth in SEQ ID NO: 4. Applicant wishes to point out that the 90 percent homology specified in Currently Amended claims 1 and 4 is well within the homology range describing functional equivalents.

In view of the arguments and amendments set forth above, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 102(e) Rejections - Jacobs et al.

The Examiner has rejected claims 1-8 under 35 U.S.C. § 102(e) as being anticipated by Jacobs *et al.* (SEQ ID NO: 6 of priority U.S. Patent Application 2001/0016650). The Examiner's rejections are respectfully traversed.

The Examiner contends that Jacobs *et al.* teach a secreted protein that was isolated from kidneys that is 99 percent identical to the claimed SEQ ID NO: 4, that this protein can be used as a pharmaceutical agent, that it can be used to treat hepatitis, and that it contains at least a signal peptide, and that portions of both the claimed and prior art proteins share 100 percent identity. The Examiner concedes that Jacobs *et al.* is silent concerning whether the prior art protein is capable of binding HBsAg preS1, if it binds to HBV particles, and if it binds to specific sequences. The Examiner asserts that the prior art protein and method meet the described properties of the claimed method in that the proteins are 99 percent identical, thus must be able to inhibit HBV infection.

Applicant very strongly disagrees with the Examiner's contention that the claimed invention is anticipated by Jacobs *et al.* Applicant wishes to respectfully point out that in fact Jacobs *et al.*, in numerous instances as described hereinbelow, emphasizes that the prior art protein has potent immunosuppressive properties, and as such very clearly teaches away from using the prior art protein for treating a pathogen infection, such as an HBV infection, such treatment obviously requiring immune stimulation, as described, for example, in the enclosed article of Whalley *et al.* Such

counter-teaching is evident, for example, at paragraph [0104], first sentence which generally states that the prior art protein exhibits immune suppressing activity. Critically, Jacobs *et al.* at paragraph [0106] teaches that the prior art protein has the capacity to down-regulate immune responses in various ways, and in particular by down-regulating T-cell mediated immune responses, which in fact are the critical type of immune responses required for treating viral infection such as HBV infection (refer, for example, to enclosed abstract of Zheng *et al.*). For example, Jacobs *et al.* at paragraphs [0105] and [0109] teach that the prior art protein may be used for treating autoimmune disorders, which are characterized by pathological immunity and inherently require immune suppression for therapy. Jacobs *et al.* at paragraphs [0107]-[0109] teach that the prior art protein suppresses B-lymphocyte functions, such as B7 activity, which are critical for activation of resting T-lymphocytes to exert anti-viral responses (refer, for example, to enclosed abstract of Zheng *et al.*). Jacobs *et al.* at paragraph [0108] teach that the prior art protein may be used for treating GVHD or transplant rejection, which similarly to autoimmunity, is caused by pathological T-lymphocyte mediated immunity and inherently requires T-lymphocyte immune suppression for therapy. Jacobs *et al.* at paragraph [0157] yet further teach that the prior art protein will exert anti-inflammatory activity, which is in fact critically required for immune elimination of pathogens such as HBV *in-vivo*. Thus, in sharp contrast to the Examiner's contention, Jacobs *et al.* in fact overwhelmingly teach against the use of the prior art protein for treatment of HBV infection.

Notwithstanding the clear counter-teachings of Jacobs *et al.*, Applicant wishes to respectfully point out that in any case at no point does Jacobs *et al.* provide any scientific results or rationale whatsoever justifying the use of the prior art protein in the treatment of any pathogen infection, such as HBV infection. The reduction to practice of Jacobs *et al.* is exclusively focused on the effects of the prior art protein on smooth muscle cell morphology and proliferation, and on the directly related vascular therapeutic applications, as clearly evident in paragraphs [0171]-[0172], the results section starting at paragraph [0182] and the legends of all of the Figures (Figures 6-11; paragraphs [0041]-[0046]) relating to the functionality of the prior art protein.

In view of the arguments and amendments set forth above, Applicant believes to have overcome the 35 U.S.C. § 102(e) rejections.

Amendments to the Specification

The nucleic acid sequence of up50 cDNA and the amino acid sequence of UP50 polypeptide are mistakenly indicated in the specification as being set forth by SEQ ID NOs: 1 and 2, respectively, at page 37, sentence starting at line 25, due to typographical error. SEQ ID NOs: 1 and 2, as shown at pages 1-4 of the Sequence Listing section, in fact set forth the nucleotide and amino acid sequences of the up43 cDNA and UP43 protein, respectively, as indicated in the specification at page 36, sentence starting at line 21, and at page 38, last paragraph. The nucleic acid sequence of up50 cDNA and the amino acid sequence of UP50 protein are in fact set forth under SEQ ID NOs: 3 and 4, respectively, at pages 4-7 of the sequence listing under SEQ ID NOs: 3 and 4, as correctly indicated in the specification at page 38, last paragraph. Applicant therefore currently elects to replace the sentence beginning at page 37, line 25, with the following typographically corrected text: "*Consequently, isolation of the complete up50 cDNA was accomplished and its cDNA sequence (SEQ ID NO: 3) and the amino acid sequence of UP50 protein (Figure 8, SEQ ID NO: 4) were determined.*"

Due to typographical errors in the sequence listing, the amino acid residue numbering coordinates of SEQ ID NO: 4 at pages 45-46 mistakenly re-start numbering from 20 at true position 25, and mistakenly start numbering at 400 at true position 385. Therefore, Applicant currently elects to replace the sequence listing in which the amino acid sequence of SEQ ID NO: 4 is defectively coordinate-numbered with the presently enclosed amended sequence listing in which the amino acid sequence of SEQ ID NO: 4 is correctly coordinate-numbered.

Statements

Applicant wishes to point out that no new matter has been introduced in the claims filed in the present communication, above.

Applicant wishes to point out that the content of the enclosed paper and computer readable copies of the sequence listing are the same and include no new matter.

In view of the amendments and remarks set forth above it is respectfully submitted that Currently Amended claims 1 and 4 are now in condition for allowance. Prompt Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,

Sol Sheinbein
Registration No. 25,457

Date: March 17, 2005

Encl.:
One month extension fee.
An amended nucleotide and amino acid sequence listing in computer readable and paper formats.
The following articles:
Article of: Le Seyec et al., 1999. J. Virol. 73:2052-2057; and
Article of: Whalley SA. *et al.*, 2001. J Exp Med. 193:847-853;
The following abstracts:
Abstract of: Bertoletti A. and Ferrari C., 2003. Hepatology 38:4-13;
Abstract of: de Man *et al.*, 1993. Neth J Med. 43:74-82;
Abstract of: Mosier DE., 2000. Immunol Res. 21:253-8;
Abstract of: Sharma *et al.*, 2004. Curr Top Med Chem. 4:895-919; and
Abstract of: Zheng BJ. *et al.*, 2004. J Viral Hepat. 11:217-24; and